## REMARKS

Reconsideration and allowance of the above-identified application are respectfully requested.

Claims 1, 2, 5, 6 and 8-43 are currently pending, wherein claim 1 is independent. Claims 1, 2, 5, 8-13 and 33 have been amended. Claims 3, 4, 7, 44 and 45 have been canceled, without prejudice or disclaimer.

Applicant notes with appreciation the acknowledgment by the Patent Office of the Information Disclosure Statements submitted to the Patent Office on January 5, 2006.

In the first section of the Office Action, claims 1, 2, 5, 6 and 8-43 are rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. These rejections are respectfully traversed.

Initially, the Patent Office asserts that the term "superpotentiating" is allegedly not clear, and then attempts to define the term "superpotentiating" by reference to searches on the Web and Webster's II dictionary, noting that these references "did not yield a definition for the word 'superpotentiate' or 'superpotentiating' other than what appears to be applicant's own work." [Office Action, page 2] It is respectfully submitted that the Patent Office's attempts to rely on extrinsic dictionaries to interpret terms of the claims, instead of relying upon the intrinsic teachings of the specification of the present application, is in derogation of the mandates of claim interpretation.

In *Phillips v. AWH Corp.*, 75 U.S.P.Q.2d 1321 (CA FC 2005), the Federal Circuit held that the methodology of claim interpretation in which the specification is consulted only *after* ordinary meaning or meanings of disputed claim terms is derived from a dictionary, treatise, or other source is **not** a proper approach to claim construction. Such an approach

improperly restricts the role of the specification, which is "the single best guide to the meaning of a disputed term." *Phillips*, 75 U.S.P.Q.2d at 1332. Elevating the dictionary meaning to such prominence improperly focuses inquiry on abstract meaning of words, rather than on the meaning of the claim terms within context of the patent. *Phillips*, 75 U.S.P.Q.2d at 1332-1335. Therefore, it is respectfully submitted that the Patent Office's attempted reliance on the dictionaries to determine a definition of the term "superpotentiating" is misplaced, misguided, and wholly improper, given the specific teachings of the specification of the present application.

Rather, According to M.P.E.P. § 2173.02,

> [t]he examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, *not* whether more suitable language or modes of expression are available. . . . Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. Examiners are encouraged to suggest claim language to applicants to improve the clarity or precision of the language used, **but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement.** [M.P.E.P. § 2173.02 (emphasis added)]

In addition, according to M.P.E.P. § 2173.01,

> **[a] fundamental principal contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers.** They can define in the claims what they regard as their invention essentially in whatever terms they choose **so long as any special meaning assigned to a term is clearly set forth in the specification** . . . . Applicant may use functional language, alternative expressions, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. As noted by the court in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought. [M.P.E.P. § 2173.01 (emphasis added)]

Furthermore,

> [t]he meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed . . . . **When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.** [M.P.E.P. § 2173.05(a) (emphasis added)]

Given the "latitude in the manner of expression and the aptness of terms" afforded to the Applicant, it is respectfully submitted that the aforementioned claims are clear and precise and fully comply with the requirements of 35 U.S.C. § 112, second paragraph.

As discussed above, with regard to the requirements of 35 U.S.C. § 112, second paragraph, it is respectfully noted that a fundamental tenet of the patent laws is that the definiteness of the claim language must be analyzed, not in a vacuum, but always in light of the teachings of the disclosure as it would be interpreted by one of ordinary skill in the art. Applicant's claims, interpreted in light of the disclosure, must reasonably apprise a person of ordinary skill in the art of the invention. [*see, e.g.*, M.P.E.P. § 2173.05(a)] Accordingly, the attention of the Patent Office is directed to the specification of the present application which clearly teaches that:

> [i]n practice the expected outcome would result in the analgesia, or the "pain level", experienced by a patient generally remaining the same, whilst the dosage of opioid administered to the patient is reduced or analgesia improving with the same dose of opioid. However, we have now found that in fact devazepide has a "superpotentiating" effect in combination with an opioid. Thus, **in the present invention the use of devazepide can act to enable the overall dose of opioid to be reduced or minimised, concurrent with improved analgesia, i.e. an increase in the analgesia, or a lowering of "pain level", experienced by the patient.** Indeed clinical studies have shown that the opioid dose may be reduced as much as 95% in some cases, in others as much as 75%. **Thus, the administration of a combination of an opioid and devazepide does not just retain the "pain level" experienced by a patient, but actually improves it, i.e. it is not just a case of opioid sparing or opioid potentiation, but the effect of the opioid is superpotentiated.** [present application, paragraph 0007, page 2, line 21 – page 3, line 11 (emphasis added)]

Therefore, based on at least the foregoing disclosure, it is respectfully submitted that claims 1, 2, 5, 6 and 8-43, when read in light of the specification, are clear and precise and reasonably apprise a person of ordinary skill in the art of the invention of the definition and meaning of the term "superpotentiating," in complete compliance with the mandates of 35 U.S.C. § 112, second paragraph.

The Patent Office further asserts that "the data in the specification do not support both reducing the opioid dosage while increasing the pain relief experienced by the patient." [Office Action, page 2] In particular, the Patent Office alleges that "[n]othing is disclosed regarding increased pain relief." [Office Action, page 3] Applicant respectfully traverses such comments, and respectfully submits that the Patent Office is in error.

Again, the attention of the Patent Office is directed to the specification of the present application which clearly teaches that:

> [a] research programme has included a double blind, double dummy, randomised, crossover study of a single dose of either 1.25 mg devazepide, 5.0 mg devazepide or placebo. Patients who took part in the study had pain with a neuropathic element, and were taking regular doses of strong opioids . . . . [present application, page 13, paragraph 0034, lines 5-8] The primary objective of this study was to compare descriptive and visual analogue scale (VAS) assessments of pain and pain relief in patients with neuropathic pain . . . . [present application, page 14, paragraph 0036, lines 3-5] At weekly intervals for the first eight weeks and at monthly intervals thereafter, patients recorded pain and global pain relief using VAS and descriptive pain questionnaires. The questionnaires were returned to the Investigator at the monthly visits. [present application, page 15, paragraph 0040, lines 1-4 (emphasis added)]

As for the results of the study, the specification of the present application clearly teaches that:

> [s]eventeen patients elected to stay on devazepide by entering the continuation study and received devazepide at 1.25 mg, 2.5 mg or 5.0 mg twice daily for up to 26 weeks. Of these patients, **ten appeared to achieve long-term pain**

> **relief (5-26 weeks) with devazepide**. Despite the requirement to remain on stable, regular doses of opioids at the dose prescribed by the investigator, **several patients . . . markedly reduced their daily opioid dose**. [present application, page 15, paragraphs 0042 and 0043 (emphasis added)]

The attention of the Patent Office is also directed to Figure 1 of the present application, which "illustrates the trend with a weaker opioid, dihydrocodeine." [present application, page 15, paragraph 0044, line 20, and Figure 1] Therefore, contrary to the assertions of the Patent Office, it is respectfully submitted that the specification of the present application clearly supports both reducing the opioid dosage while increasing the pain relief experienced by the patient.

The Patent Office additionally asserts that "the data only support opioids, not all analgesics." Applicant respectfully traverses such comments, and respectfully submits that the Patent Office is in error.

Once more, the attention of the Patent Office is directed to the specification of the present application which clearly teaches that:

> [p]atients were stabilised on morphine (34), oxycodone (2), fentanyl (3), methadone (1), hydromorphone (1) and diamorphine (1); with one patient taking both morphine and fentanyl. Breakthrough analgesic product use included (in addition to the above) tramadol, diclofenac, dihydrocodeine, paracetamol, codeine, aspirin, ibuprofen, dextropropoxyphene, buprenorphine, pethidine, carbamazepine, and hydromorphone (and combination products containing the above, for example; Anadin.TM. (aspirin), Anadin.TM. extra (aspirin and paracetamol), co-codamol, co-dydramol, co-proxamol, and remedeine). [present application, page 11, paragraph 0031, lines 8-14]

As noted in the present application, "[t]he analysis of specific use of breakthrough analgesia as opposed to regular opioid use was not possible because patients were taking a variety of different analgesic drugs (including opioids) in addition to their regular opioid." [present application, page 11, paragraph 0032, lines 16-18] It was further noted that "[i]t was also

difficult to define breakthrough analgesia in those patients who were using the same opioid for both regular use and for breakthrough analgesia (latter to control breakthrough pain)." [present application, page 11, paragraph 0032, lines 18-20] Consequently, "[f]or this reason, **all analgesic medication** was included in the determination of a total dose for the treatment period, irrespective of whether it was used as regular stable medication or for breakthrough pain." [present application, page 11, paragraph 0032, lines 20-23 (emphasis added)] Therefore, contrary to the assertions of the Patent Office, it is respectfully submitted that Patent Office's statement that "the data only support opioids" is clearly contradicted by the teachings of the specification of the present application.

For at least the foregoing reasons, it is respectfully submitted that claims 1, 2, 5, 6 and 8-43 are clear and precise, in full and complete compliance with the mandates of 35 U.S.C. § 112, second paragraph. Accordingly, reconsideration and withdrawal of these grounds of rejection are respectfully requested.

However, merely to facilitate prosecution in the present application and not for any purpose related to patentability, Applicant hereby amends independent claim 1 to recite a method of reducing the amount of an opioid administered to a patient, including the step of administering to the patent a therapeutically effective amount of the opioid and a potentiating amount of devazepide, wherein upon subsequent treatments the amount of the opioid is reduced by an amount of from about 25% to about 95% by weight of the amount of the opioid required in the absence of the devazepide. Support for such an amendment can be found in the present application in original claims 4 and 7, on page 3, paragraph 0007, lines 4-11, and in Table 2, particularly with references to patients "ap06/05" and "gg01/01." Dependent claims 2, 5, 8-13 and 33 have been amended merely to ensure consistency of the

language between these dependent claims and independent claim 1, and merely to make minor grammatical changes to clarify the language of these claims. No new matter has been introduced by way of these amendments.

In the second section of the Office Action, claims 1, 2, 5, 6 and 8-43 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Panos et al. (International Publication No. WO 99/18967, hereinafter "Panos"). In addition, claims 1, 2, 5, 6 and 8-43 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Dourish et al. (The Journal of Pharmacology and Experimental Therapeutics, Vol. 255, No. 3, 1990, pages 1158-1164, hereinafter "Dourish"). These rejections are respectfully traversed.

As discussed in the Amendment dated November 15, 2005, and as acknowledged in the background section of the present application, devazepide in combination with an opioid analgesic potentiates the analgesic effect of the overall dose of the opioid. In practice, a level of pain that is refractory-to-opioid is experienced despite a given dose of opioid, thus devazepide is added to the opioid regimen. "[T]he expected outcome would result in the analgesia, or the 'pain level', experienced by a patient generally remaining the same, whilst the dosage of opioid administered to the patient is reduced or analgesia improving with the same dose of opioid." [present application, paragraph 0007, page 2, line 21 – page 3, line 2]

However, what has been unexpectedly observed in accordance with exemplary embodiments of the present invention is that the use of devazepide can act not only to enable the overall dose of opioid to be reduced or minimized, but that this is surprisingly "**concurrent with improved analgesia**, i.e. an increase in the analgesia, or a lowering of 'pain level', experienced by the patient. Indeed clinical studies have shown that the opioid dose may be reduced as much as 95% in some cases, in others as much as 75%. Thus, the

administration of a combination of an opioid and devazepide does not just retain the 'pain level' experienced by a patient, but actually **improves** it, i.e. it is not just a case of opioid sparing or opioid potentiation, but the effect of the opioid is superpotentiated." [present application, paragraph 0007, page 3, lines 5-11]

In other words, the expected or predictable outcomes for devazepide being added to an opioid dosing regimen are either: 1.) the level of pain goes down and the dose of opioid stays the same; or 2.) the level of pain stays the same and the dose of opioid goes down. However, what has been observed and would **not** be expected or predicted is that the level of pain goes down **accompanied** by the dose of opioid going down. This phenomenon has been termed '**super**potentiation' in the present application in order to differentiate it from the previously-observed potentiation effects of devazepide. Indeed, this phenomenon is substantiated in the clinical data of Table 2, and in particular reference to the patient referred to as "ap06/05," where it is shown that pain relief was accompanied by a reduction of 54% in the tramadol dose. Further unpublished clinical trial data supports the observation of pain levels going down with accompanied reduction in opioid dose.

It is upon this hitherto unobserved and unexpected result that the present application is based, i.e., the combination of CCK antagonist plus opiate analgesic does **more** than merely reduce the dose of opiate needed, but provides a qualitative improvement in pain relief not obtainable by simply increasing the dose of opiate. It is respectfully submitted that this phenomenon is not obvious from the prior art.

In contrast, Panos is discussed in the present application as follows:

> WO 99/18967 discloses the administration of devazepide in combination with an opioid analgesic so as to potentiate the analgesic effect of the overall dose of the opioid. In practice the expected outcome would result in the analgesia, or the "pain level", experienced by a patient generally remaining the same,

> whilst the dosage of opioid administered to the patient is reduced or analgesia improving with the same dose of opioid." [present application, paragraph 0007, page 2, line 19 – page 3, line 2]

As understood by Applicant, Panos teaches fixed pharmaceutical compositions of an opioid-potentiating amount of a CCK antagonist and an analgesic amount of an opioid with a biphasic carrier. It is respectfully submitted that Panos made no investigation into the effect of devazepide when the dose of opioid is altered/moderated. Thus, it is respectfully noted that Panos teaches option 2 of the predicted outcomes described above, i.e., the level of pain stays the same and the dose of opioid goes down.

It is respectfully submitted that Panos does not teach, suggest or could be used to predict that devazepide itself can act to enable the overall dose of the opioid to be reduced or minimized, concurrent with improved analgesia, i.e., an increase in the analgesia, or a lowering of "pain level," experienced by the patient. It is further respectfully submitted that Panos does not teach or suggest that devazepide acts as a synergist allowing both a reduction in the opioid dose while increasing the effect of the analgesic, i.e., the level of pain goes down **accompanied** by the dose of opioid going down. Furthermore, Panos does not teach or suggest that the amount of opioid can be reduced by between about 25 to about 95% by weight. Therefore, it is respectfully submitted that Panos does not render the subject matter of independent claim 1 obvious.

As understood by Applicant, Dourish teaches that there was **no analgesic effect of devazepide per se**. [*see* Dourish, page 1160, column 2, under the paragraph beginning "Effect of devazepide on pain thresholds"] In other words, devazepide has no intrinsic antinociceptive properties. Furthermore, the first three lines of text on page 1160, column 2 of Dourish state that (following the determination of the antinociceptive effect of morphine in

this model) "[a] dose of 0.1 mg/kg of morphine was chosen as a sub-threshold dose to be used in the subsequent interaction experiments." [Dourish, page 1160, column 2 (emphasis added)] It is respectfully submitted that there is no investigation in Dourish into the effect of devazepide when the dose of opioid is altered/moderated. Rather, it is investigated at a sub-threshold level. In addition, Dourish does not teach or suggest that the amount of opioid can be reduced by between about 25 to about 95% by weight. Therefore, it is respectfully submitted that Panos does not render the subject matter of independent claim 1 obvious.

According to M.P.E.P. § 2143, to establish a prima facie case of obviousness, three basic criteria must be met. In particular, "the prior art reference (or references when combined) must teach or suggest **all** of the claim limitations." [M.P.E.P. § 2143 (emphasis added)] It is respectfully submitted that neither Panos nor Dourish, whether considered individually or in combination, teach a method of reducing the amount of an opioid administered to a patient, including the step of administering to the patent a therapeutically effective amount of the opioid and a potentiating amount of devazepide, wherein upon subsequent treatments the amount of the opioid is reduced by an amount of from about 25% to about 95% by weight of the amount of the opioid required in the absence of the devazepide, as recited in independent claim 1 of the present application.

In addition, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." [M.P.E.P. § 2143] In other words, "[o]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge

generally available to one of ordinary skill in the art." [M.P.E.P. § 2143.01] It is respectfully submitted that there is absolutely no teaching, suggestion, or motivation, either explicitly or implicitly, to modify the references in the manner suggested by the Patent Office or to combine the reference teachings.

For at least the aforementioned reasons, it is respectfully submitted that Panos and Dourish, whether considered individually or in combination, do not render the subject matter of independent claim 1 obvious.

It is noted that the Patent Office once again asserts that "[t]he data in the specification is persuasive only for 'potentiating,' and not for the level of pain going down accompanied by the dose of opioid going down." [Office Action, page 3] For at least those reasons discussed previously with respect to the Patent Office's statements made in the first section of the Office Action, Applicant respectfully traverses such comments, and respectfully submits that the Patent Office is in error.

Dependent claims 2, 5, 6 and 8-43 depend from independent claim 1 and are, therefore, patentably distinguishable over Panos and Dourish, whether considered alone or in combination, for at least those reasons stated above with regard to independent claim 1.

For at least the foregoing reasons, it is respectfully submitted that Panos and Dourish, whether considered alone or in combination, do not render the subject matter of claims 1, 2, 5, 6 and 8-43 unpatentable.

All of the rejections raised in the Office Action having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. Should the Examiner have any questions regarding this amendment or the application in general, the Examiner is urged to contact the Applicant's attorney, Andrew J. Bateman, by telephone at (202) 625-3547. All correspondence should continue to be directed to the address given below.

Respectfully submitted,

By: Andrew J. Bateman

Andrew J. Bateman
Attorney for Applicant
Registration No. 45,573

PATENT ADMINISTRATOR
KATTEN MUCHIN ROSENMAN LLP
1025 Thomas Jefferson Street, N.W.
East Lobby, Suite 700
Washington, DC 20007-5201
Facsimile No.: (202) 298-7570
Customer No.: 27160